Available online at www.sciencedirect.com
SCIENCE DIRECT®
Neuropharmacology 46 (2004) 1097–1104
NEURO PHARMACOLOGY
www.elsevier.com/locate/neuropharm

Topiramate selectively protects against seizures induced by ATPA, a GluR5 kainate receptor agonist

Rafal M. Kaminski, Madhumita Banerjee, Michael A. Rogawski *

Epilepsy Research Section, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892, USA

Received 4 September 2003; received in revised form 14 January 2004; accepted 3 February 2004

Abstract

Although the mechanism of action of topiramate is not fully understood, its anticonvulsant properties may result, at least in part, from an interaction with AMPA/kainate receptors. We have recently shown that topiramate selectively inhibits postsynaptic responses mediated by GluR5 kainate receptors. To determine if this action of topiramate is relevant to the anticonvulsant effects of the drug in vivo, we determined the protective activity of topiramate against seizures induced by intravenous infusion of various ionotropic glutamate receptor agonists in mice. Topiramate (25–100 mg/kg, i.p.) produced a dose-dependent elevation in the threshold for clonic seizures induced by infusion of ATPA, a selective agonist of GluR5 kainate receptors. Topiramate was less effective in protecting against clonic seizures induced by kainate, a mixed agonist of AMPA and kainate receptors. Topiramate did not affect clonic seizures induced by AMPA or NMDA. In contrast, the thresholds for tonic seizures induced by higher doses of these various glutamate receptor agonists were all elevated by topiramate. Unlike topiramate, carbamazepine elevated the threshold for AMPA- but not ATPA-induced clonic seizures. Our results are consistent with the possibility that the effects of topiramate on clonic seizure activity are due to functional blockade of GluR5 kainate receptors. Protection from tonic seizures may be mediated by other actions of the drug. Together with our in vitro cellular electrophysiological results, the present observations strongly support a unique mechanism of action of topiramate, which involves GluR5 kainate receptors.
Published by Elsevier Ltd.

Keywords: Topiramate; Carbamazepine; GluR5; AMPA; Kainate; NMDA; Seizure; Mouse

1. Introduction

Topiramate is one of several newer antiepileptic drugs (AEDs) that were introduced in the 1990s. The drug is effective against both partial and generalized seizures, and may also be useful in some intractable childhood epilepsies (Bazil, 2002; Deckers et al., 2003). In addition, topiramate may be beneficial in the treatment of a host of neuropsychiatric syndromes including bipolar disorder (Ernst and Goldberg, 2003), migraine (Von Seggern et al., 2002), neuropathic pain (Chong and Libretto, 2003) and alcohol dependence (Johnson et al., 2003). Topiramate's neuroprotective properties in experimental models make it a potential candidate for stroke treatment (Edmonds et al., 2001; Smith-Swintosky et al., 2001; Angehagen et al., 2003b).

As a sulfamate derivative of the naturally occurring monosaccharide D-fructose, topiramate is structurally distinct from other AEDs. The spectrum of pharmacological actions of topiramate is also different from those of other AEDs (Shank et al., 1994, 2000). While the cellular mechanisms underlying the anticonvulsant activity of topiramate are not fully defined, the drug has several actions that could account for its antiepileptic efficacy, including inhibitory effects on AMPA/kainate-type ionotropic glutamate receptors (Gibbs et al., 2000; Skradski and White, 2000), blockade of voltage-activated Na^+ (Zona et al., 1997; Taverna et al., 1999) and Ca^{2+} channels (Zhang et al., 2000), and positive modulatory effects on $GABA_A$ receptors (White et al., 1997, 2000). In addition, topiramate inhibits carbonic anhydrase isoenzymes (Dodgson et al., 2000), although this action is not believed to

* Corresponding author. Tel.: +1-301-496-8013.
E-mail address: michael.rogawski@nih.gov (M.A. Rogawski).

0028-3908/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.neuropharm.2004.02.010

contribute to its clinical efficacy. It has been hypothesized that the effects of topiramate on the various receptors and ion channels that it modulates may be mediated by a common mechanism related to protein phosphorylation (Shank et al., 2000; Angehagen et al., 2003a).

Topiramate is the only marketed AED that inhibits AMPA/kainate receptor currents at clinically relevant concentrations (Rogawski, 2002). The initial discovery that topiramate blocks AMPA/kainate receptors was based on studies with the nonselective agonist kainate in cultured neurons (Gibbs et al., 2000). More recently, we have found that topiramate selectively inhibits GluR5 kainate receptor currents in the amygdala slice, and is relatively weaker and less efficacious as an antagonist of AMPA receptor currents (Gryder and Rogawski, 2003). In the present study, we sought to determine if the selectivity of topiramate at the synaptic level in in vitro slice recordings is relevant to the anticonvulsant effects of the drug in vivo. It has been observed that pharmacological antagonists of ionotropic glutamate receptors selectively block seizures induced by administration of excitatory amino acids that activate the relevant receptors (Singh et al., 1991; Steppuhn and Turski, 1993). Accordingly, we determined the protective activity of topiramate against seizures induced by intravenous infusion in mice of various ionotropic glutamate receptor agonists, including (*RS*)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propanoic acid (ATPA), a selective agonist of GluR5 kainate receptors (Arnt et al., 1995; Clarke et al., 1997). Our results are consistent with the concept that the in vivo anticonvulsant activity of topiramate is mediated, at least in part, by effects on GluR5 kainate receptors.

2. Materials and methods

2.1. Animals

Male NIH Swiss mice, weighing 25–30 g, were housed five per cage with free access to food and water in a vivarium with controlled temperature (22–26 °C), humidity (40–50%) and lighting (artificial 12 h light/dark cycle). All animals were allowed to acclimate for at least 5 days before testing. The experiments were performed during the light cycle after at least 30 min acclimation to the experimental room. The animal facilities were fully accredited by the American Association for Accreditation of Laboratory Animal Care and the experiments were performed under a protocol approved by the National Institute of Neurological Disorders and Stroke Animal Care and Use Committee, in full compliance with the Guide for Care and Use of Laboratory Animals of the National Research Council (National Academy Press, Washington, DC, 1966).

2.2. Drugs

The following convulsant substances were used: (i) (*RS*)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)-propanoic acid (ATPA); (ii) (*RS*)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid hydrobromide (AMPA); (iii) *N*-methyl-D-aspartic acid (NMDA); (iv) kainic acid [kainate; (2*S*,3*S*,4*R*)-carboxy-4-(1-methylethenyl)-3-pyrrolidineacetic acid]. ATPA and AMPA were from Tocris (Ellisville, MO), NMDA was from RBI (Natick, MA), and kainate was from Sigma (St. Louis, MO). AMPA, NMDA and kainate were dissolved in phosphate buffered saline (PBS). ATPA was dissolved in a 5% solution of β-cyclodextrin (CDT Inc., High Springs, FL) in PBS. Topiramate [2,3:4,5-*bis*-*O*-(1-methyl-ethylidene)-36-D-fructopyranose sulfamate], kindly provided by Johnson & Johnson Pharmaceutical Research and Development (Spring House, PA), and carbamazepine (Sigma) were dissolved in a 25% aqueous solution of polyethylene glycol (Sigma).

2.3. Intravenous catheterization and infusion of glutamate receptor agonists

Each mouse was placed in a Rotating Tail Injector (Braintree Scientific, Braintree, MA), which is a plastic cylinder (4.5-in. long, 1.2-in. inner diameter) with a plunger for restraint. Lidocaine was applied on the tail before catheterization to decrease pain during the procedure and the lateral tail vein was catheterized with a 0.5-in. long 30-gauge needle attached to a 12-in. length of polyethylene tubing (PE-10). Correct needle placement was verified by the appearance of blood in the tubing. The needle was gently secured to the tail using plastic tape. The tubing was attached to a 12-ml plastic syringe containing the convulsant solutions. The syringe was mounted on an infusion pump (Harvard Apparatus, South Natick, MA). Following catheterization, unrestrained mice were placed in Plexiglas cages (11 in. × 8 in. × 6 in.) for behavioral observation during the infusion. The infusion rate was 0.5 ml/min and the concentrations of all the glutamate receptor agonists were 0.025 mmol/ml. These parameters, chosen from among those previously shown to permit reliable assessment of the seizure threshold (Steppuhn and Turski, 1993), minimized the infusion time, thus limiting the discomfort. Topiramate or carbamazepine (0.01 ml/g body weight) were injected i.p. 30 min before infusion of the convulsant substances.

2.4. Assessment of seizure threshold

Two signs of seizure activity that typically occur in sequence during agonist infusion were used to determine the threshold for seizure induction: (i) clonus (repeated jerking movements of all four limbs) with loss of the righting reflex, and (ii) tonic hindlimb extension. The times between the start of the infusion and the onset of these endpoints were recorded. The threshold doses (TD) of the glutamate receptor agonists (in mmol/kg) for each endpoint were calculated as follows: TD = (infusion duration [s] × infusion rate [ml/min]× drug concentration [mg/ml] × 1000)/(60 [s] × weight of mouse [g] × molecular weight). Our protocol permitted a maximum infusion time of 4 min, but the infusion times required to reach both seizure signs never exceeded 3.5 min (except for NMDA where some animals did not exhibit tonic seizure activity).

2.5. Data analysis

The mean TD values in treatment groups [taken to be an estimate of the convulsant dose for 50% of animals (CD_{50})] were compared using one-way analysis of variance (ANOVA) for each seizure endpoint, followed, when appropriate, by Dunnett's test, or in cases where there were only two groups to compare, using the unpaired Student's *t*-test. For graphical display (Fig. 1), TD values in each group are plotted against the cumulative fraction of animals in that group exhibiting the seizure sign at equal or lower doses. The data points are fit to the following approximation of a cumulative normal distribution $F = 50[1 + \mathrm{erf}(\mathrm{TD} - \mathrm{CD}_{50})/\sqrt{2\sigma}]$, where F is the fraction of animals (in percent) and CD_{50} and σ are the mean and standard deviation with the σ value constrained to be equal for the clonus and tonus data sets.

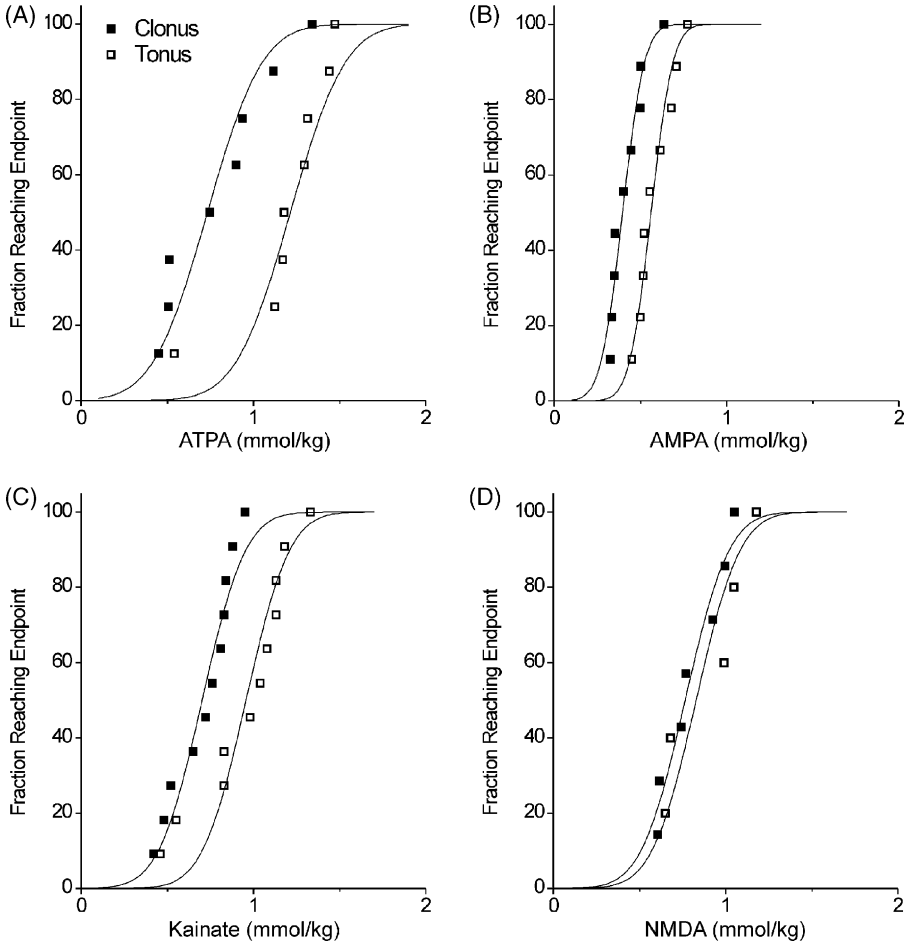

Fig. 1. Induction of clonic and tonic seizure activity by glutamate receptor agonists. ATPA (A), AMPA (B), kainate (C) or NMDA (D) was infused (0.5 ml/min) through the lateral tail vein at a concentration of 0.025 mmol/ml. During the infusion, mice exhibited clonic convulsions (clonus) which progressed to tonic hindlimb extension (tonus). The dose at which each of 7–11 animals tested per group exhibited the seizure signs was calculated from the time of infusion and is plotted in a cumulative fashion as a percent of total number of animals tested. Two of the animals treated with NMDA exhibited clonic seizures only prior to expiring. The data points are fit to a cumulative normal distribution function as described in "Materials and methods". The CD_{50} values derived from these data are presented in Table 1.

Potencies of topiramate for antagonizing seizure signs induced by the various agonists were compared by estimating a dose of topiramate expected to produce a theoretical (not necessarily achievable) doubling of the agonist CD_{50} value (A_2). Ratios of agonist CD_{50} values in the presence and absence of topiramate (R) were calculated and $\log_{10}(R-1)$ was plotted against the $\log_{10}$ (topiramate dose). A_2 was then taken to be $10^{-B/m}$ where B is the y-intercept and m is the slope of the best-fit straight line. In this analysis, only the rising phase of the dose–response curves was considered.

3. Results

Intravenous injection of all four glutamate receptor agonists induced a sequence of clonus followed by tonus. For ATPA, kainate and NMDA the latencies for the clonic and tonic phases were 50–150 and 130–170 s; for AMPA the corresponding latencies were 40–65 and 55–80 s. Molar doses of the agonists associated with each endpoint were determined from the latencies as described in "Materials and methods". Threshold values for the agonists are presented in Fig. 1 and CD_{50} values derived from these data are given in Table 1. It is noteworthy that all four agonists have molar potencies within the same range, although AMPA is modestly more potent. In addition, the CD_{50} values for clonus are in all cases significantly lower than those for tonus, except for NMDA, which induced tonus at nearly the same dose range as clonus. In contrast to the other agonists that invariably elicited tonic seizure activity with increased agonist doses, only five of seven animals treated with NMDA exhibited tonus. The remainder expired as the dose of NMDA was increased without demonstrating tonus.

Topiramate was tested for its ability to protect against clonic and tonic convulsions by determining the thresholds for the two behavioral signs after pretreatment with the drug. As shown in Fig. 2A, pretreatment with topiramate at doses of 25, 50 and 100 mg/kg caused a dose-dependent increase in the thresholds for ATPA-induced clonic [$F(3,25)=5.7$; $p=0.005$] and tonic [$F(3,25)=14.4$; $p<0.001$] convulsions. Animals pretreated with topiramate at 50 and 100 mg/kg had significantly higher thresholds for both clonic and tonic seizures as compared with vehicle-pretreated animals ($p<0.05$; Dunnett's test). In contrast, the thresholds for AMPA-induced clonic seizures remained unchanged after topiramate (25–100 mg/kg) pretreatment [$F(3,25)=1.25$; $p=0.3$], although the thresholds for tonic seizures were increased [$F(3,25)=6.2$; $p=0.003$] (Fig. 2B). While topiramate raised the threshold for tonic seizures in comparison with vehicle at all doses tested ($p<0.05$; Dunnett's test), the effect was not dose-dependent.

Topiramate pretreatment (50–200 mg/kg) caused a small, but significant, increase in the threshold for kainate-induced clonic seizures [$(F(4,36)=3.0$; $p=0.033$] (Fig. 2C). The threshold for tonic seizures was more strongly affected [$F(4,36)=9.5$; $p<0.001$)]. For both tonic and clonic kainate-induced seizures, topiramate exhibited an inverted U-shaped dose–response curve with a reduction in activity at the highest doses tested. Similar reductions in topiramate efficacy at higher doses have been observed previously in other models (R.P. Shank, personal communication). For clonic seizures, only the effects at the 50 and 100 mg/kg doses reached statistical significance ($p<0.05$; Dunnett's test), whereas for tonic seizures significant effects were obtained at 50, 100 and 200 mg/kg.

Topiramate pretreatment did not affect the threshold for NMDA-induced clonic seizures [$(F(3,24)=0.16$; $p=0.9$] (Fig. 2D). However, it completely prevented the occurrence of NMDA-induced tonic seizures at all doses tested; the animals expired as the NMDA infusion continued without exhibiting tonus.

The estimated doses of topiramate for producing a two-fold increase in tonic seizure threshold (A_2) are 210, 210, 200 mg/kg for ATPA, AMPA and kainate, respectively, demonstrating a nearly identical sensitivity of the tonic seizures irrespective of the agonist. (An estimate of tonic-seizure A_2 value for NMDA was not attempted since tonic seizures were not always observed, even with vehicle pretreatment.) In contrast, for the clonic seizure endpoint, only ATPA exhibited a rising topiramate dose–response relationship for mean threshold values that differed significantly from vehicle; its A_2 value was 315 mg/kg.

To confirm the specificity of topiramate, studies were carried out with the reference AED carbamazepine at a dose (20 mg/kg) that is effective in anticonvulsant screening models (Swinyard et al., 1989). As shown in Fig. 3A, pretreatment with this dose of carabamazepine did not raise the threshold for ATPA-induced clonic seizures, although it provided complete protection against tonic seizures. In contrast, carbamazepine significantly raised the threshold for both AMPA-induced clonic seizures and tonic seizures

Table 1
Threshold dose values for induction of seizure signs by intravenous excitatory amino acid agonists

Agonist	CD_{50} (mmol/kg) (±SEM)	
	Clonus	Tonus
ATPA	0.81 ± 0.11	1.19 ± 0.10*
AMPA	0.42 ± 0.03	0.59 ± 0.04*
Kainate	0.71 ± 0.05	0.96 ± 0.08*
NMDA	0.81 ± 0.07	0.91 ± 0.10

CD_{50} values were determined as described in "Materials and methods" from the data presented in Fig. 1.

* Significantly different from clonus value.

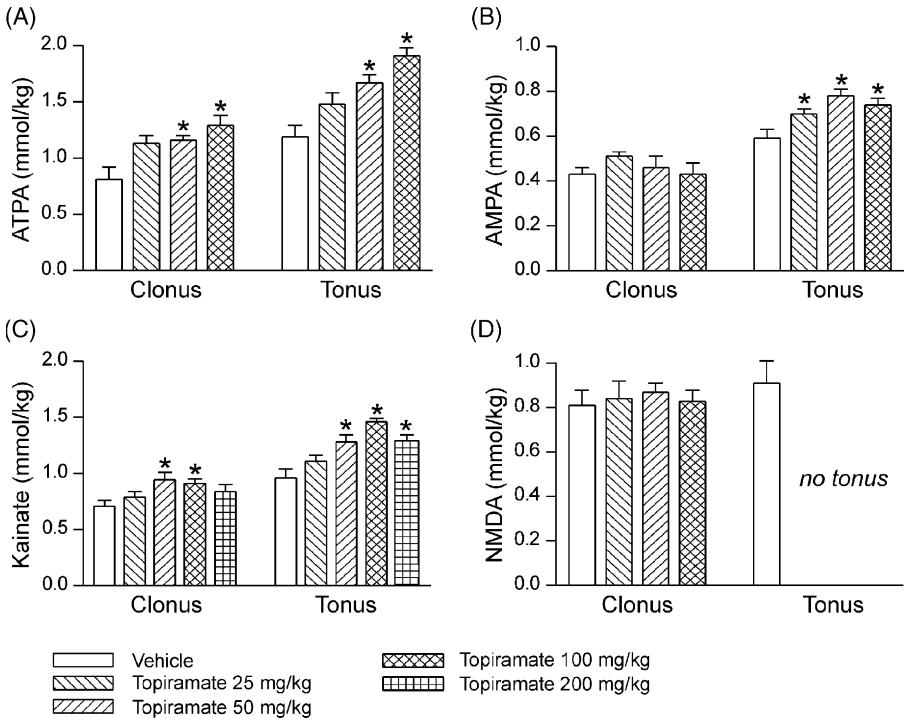

Fig. 2. Effects of topiramate on convulsant thresholds of glutamate receptor agonists. ATPA (A), AMPA (B), kainate (C) or NMDA (D) was infused (0.5 ml/min) through the lateral tail vein at a concentration of 0.025 mmol/ml. Vehicle or topiramate at the doses indicated was injected i.p. 30 min before the start of infusion. During the infusion, mice exhibited clonic convulsions (clonus) which progressed to tonic hindlimb extension (tonus), except for some animals receiving NMDA (two of seven vehicle-pretreated animals did not exhibit tonus and were not included in the calculation of the threshold and none of the topiramate-pretreated animals exhibited tonus). Animals receiving NMDA generally died within 2–3 min of the onset of the NMDA infusion, but in two of five mice treated with 100 mg/kg topiramate, the mice survived the maximum 4-min infusion time without tonus. The threshold dose for each seizure endpoint was calculated from the infusion duration (see "Materials and methods"). Each bar represents the mean ± SEM of the threshold values (CD_{50}s) from 5 to 11 animals. For each agonist, the CD_{50} values were compared using one-way analysis of variance (ANOVA) followed, when appropriate, by Dunnett's test. ∗Significantly different from vehicle ($p < 0.05$).

(Fig. 3B). The threshold for kainate-induced clonic seizures was also raised, but this did not reach statistical significance, whereas there was a significant elevation of the tonic seizure threshold (Fig. 3C). Carbamazepine did not raise the clonic seizure threshold for NMDA but it did eliminate tonic seizures (Fig. 3D).

4. Discussion

The key experimental observation in this study is that clonic seizures induced by the selective GluR5 kainate receptor agonist ATPA were blocked in a dose-dependent fashion by topiramate. Topiramate was also protective against clonic seizures induced by the mixed AMPA/kainate receptor agonist kainate. The drug did not affect clonic seizures induced by AMPA which is only very weakly active as a kainate receptor agonist (Fletcher and Lodge, 1996) and NMDA which does not act as a kainate receptor agonist. These results strongly support the conclusion, developed from in vitro cellular neurophysiological studies (Gryder and Rogawski, 2003), that topiramate acts as a potent functional antagonist of GluR5 kainate receptors and demonstrates that this in vitro activity is relevant to the anticonvulsant activity of the drug in vivo.

ATPA is a *tert*-butyl analog of AMPA originally reported to have weak AMPA receptor agonist activity (Lauridsen et al., 1985; Bleakman et al., 2002). However, more recent studies revealed that ATPA is a far more potent agonist at homomerically (Clarke et al., 1997) and heteromerically (Cui and Mayer, 1999) expressed GluR5 kainate receptors. Indeed, ATPA is 29–94% less potent as an agonist of homomeric AMPA receptors expressed in *Xenopus* oocytes and only 7–22% as efficacious for activating ionic currents (Stensbøl et al., 1999). Inasmuch as topiramate failed to affect clonic seizures induced by intravenous AMPA, a selective agonist of AMPA receptors that induces desensitizing responses (Fletcher and Lodge, 1996), our results support the idea that the convulsant activity of ATPA at doses just sufficient to produce clonic seizures largely resides in its GluR5 kainate receptor agonist activity and not in its weak AMPA receptor activity.

Kainate is a nonselective agonist of kainate-type glutamate receptors, which, unlike ATPA, activates kai-

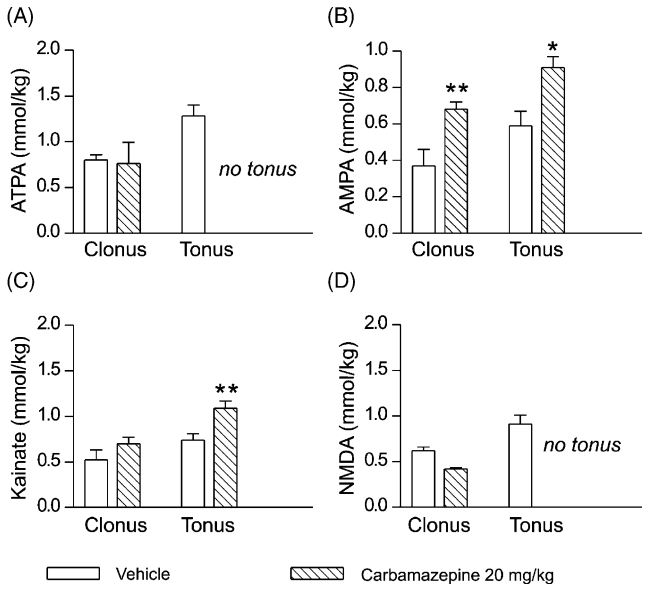

Fig. 3. Effects of carbamazepine on convulsant thresholds of glutamate receptor agonists. ATPA (A), AMPA (B), kainate (C) or NMDA (D) was infused (0.5 ml/min) through the lateral tail vein at a concentration of 0.025 mmol/ml. Vehicle or carbamazepine was injected i.p. 30 min before the start of infusion. Each bar represents the mean ± SEM of the threshold values (CD_{50}s) from three to five animals. ATPA and NMDA animals receiving carbamazepine survived the maximum 4 min infusion time without tonus. For each agonist, the CD_{50} values were compared using Student's *t*-test. *Significantly different from vehicle ($p < 0.05$); **Significantly different from vehicle ($p < 0.01$); other comparisons did not reach statistical significance ($p > 0.05$).

nate receptors containing both of the major low-affinity kainate receptor subunits GluR5 and GluR6 (Sommer et al., 1992). In addition, kainate activates AMPA receptor responses (Chittajallu et al., 1999). Although kainate is substantially less potent as an agonist at AMPA receptors than at kainate receptors, it is functionally highly active at AMPA receptors because the responses it induces are non-desensitizing (Boulter et al., 1990; Stein et al., 1992; Fletcher and Lodge, 1996). The identity of the kainate receptors relevant to the convulsant activity of kainate has been assessed in studies with mice engineered to lack either the GluR5 or GluR6 kainate receptor subunits (Mulle et al., 1998). These studies support the view that kainate receptors containing the GluR6 subunit contribute in a substantial way to the convulsant effects of kainate. In addition, it is likely that the agonist activity of kainate at AMPA receptors also contributes to kainate-induced convulsions. Topiramate raised the threshold for clonic seizures induced by kainate, although less dramatically so than for ATPA and the effect was not dose-dependent. This weak activity could be due, in part, to blockade of kainate receptors by topiramate. Since kainate-induced seizures may principally reflect activation of GluR6 kainate receptors, our results suggest that topiramate may block GluR6-containing kainate receptors in addition to those containing GluR5. To date, the action of topiramate on GluR6 kainate receptors has not been extensively investigated in in vitro studies: one preliminary report indicated a weak blocking action (Ghetti et al., 2001), whereas another did not (Smith et al., 2000). The relatively weak effect of topiramate against kainate-induced seizures (compared with the effect on ATPA) could therefore be due to its lower activity against GluR6 containing kainate receptors than GluR5 kainate receptors, a point that requires further confirmation, or to its low potency and efficacy as an antagonist of AMPA receptors (Gryder and Rogawski, 2003). In fact, in the present study topiramate failed to affect clonic seizures induced by AMPA, supporting the in vitro studies showing insubstantial AMPA receptor blocking activity (Gryder and Rogawski, 2003). The lack of effect of topiramate on NMDA-induced clonic seizures is in line with a report showing that the drug does not affect NMDA receptor currents in neuronal cultures (Gibbs et al., 2000).

Although clonic convulsions emerged as the first seizure sign during intravenous infusion of all four glutamate receptor agonists, there was progression, with higher doses, to tonic hindlimb extension. The evolution from clonic to tonic seizures reflects the spread of paroxysmal activity into subcortical forebrain and brain stem structures (Gale, 1988). The tonic seizures induced by all agonists were inhibited by topiramate. As noted above, while topiramate is particularly potent as an antagonist of GluR5 kainate receptors, it does partially inhibit AMPA receptors at higher concentrations (Gryder and Rogawski, 2003). Therefore, the ability of topiramate to protect against tonic seizure activity could relate to its weak AMPA receptor blocking activity. AMPA, kainate, and ATPA at sufficiently high doses all directly activate AMPA receptors. Moreover, AMPA receptors are likely to be critical in the propagation of seizure activity (Rogawski and Donevan, 1999; Avanzini and Franceschetti, 2003). Blockade of AMPA receptors might therefore protect against the spread of seizure activity resulting in tonic hindlimb extension, even if they are triggered by an agonist like NMDA that does not directly activate AMPA receptors. Alternatively, other actions of topiramate could specifically inhibit tonic seizure activity. For example, topiramate has been shown to have effects on voltage-activated Na^+ channels (Zona et al., 1997; Taverna et al., 1999), like several other antiepileptic agents that are well recognized to block tonic hindlimb extension (Rogawski, 2002).

We carried out comparative studies with the AED carbamazepine to determine whether selective effects on ATPA and not AMPA-induced clonic seizures is a unique characteristic of topiramate. Indeed, carbamazepine has previously been shown to raise the threshold

for seizures induced by infusion of ATPA (Steppuhn and Turski, 1993) and AMPA (Yamashita et al., 2004) into the mouse lateral ventricle. However, we found that carbamazepine did not affect the threshold for clonic seizures induced by systemic ATPA at a dose that was highly effective in raising the threshold for AMPA-induced clonic seizures. Consequently, carbamazepine, in contrast to topiramate, does not act as a selective functional GluR5 kainate receptor antagonist, highlighting the novel pharmacological activity of topiramate.

In conclusion, by assessing blockade of seizure activity induced by intravenous administration of ionotropic glutamate receptor agonists, we have obtained support for the concept that topiramate selectively inhibits GluR5 kainate receptor responses in vivo. The doses of topiramate that protect against ATPA-induced clonic seizure are similar to those that are effective in other seizure models in the mouse; such doses are believed to be associated with blood concentrations comparable to those obtained in humans receiving therapeutic doses of the drug (R.P. Shank, personal communication). Consequently, blockade of GluR5 kainate receptors could in part be responsible for topiramate's broad clinical anticonvulsant efficacy as well as its beneficial effects in non-epileptic conditions. Other actions, including those on Na^+ channels, are also likely to contribute to the overall effectiveness of topiramate. Nevertheless, the present results add to the emerging evidence that GluR5 kainate receptors are a promising novel target for AED development (Smolders et al., 2002; Rogawski et al., 2003).

References

Angehagen, M., Ben Menachem, E., Ronnback, L., Hansson, E., 2003a. Novel mechanisms of action of three antiepileptic drugs, vigabatrin, tiagabine, and topiramate. Neurochemical Research 28, 333–340.

Angehagen, M., Ben Menachem, E., Ronnback, L., Hansson, E., 2003b. Topiramate protects against glutamate- and kainate-induced neurotoxicity in primary neuronal-astroglial cultures. Epilepsy Research 54, 63–71.

Arnt, J., Sanchez, C., Lenz, S.M., Madsen, U., Krogsgaard-Larsen, P., 1995. Differentiation of in vivo effects of AMPA and NMDA receptor ligands using drug discrimination methods and convulsant/anticonvulsant activity. European Journal of Pharmacology 285, 289–297.

Avanzini, G., Franceschetti, S., 2003. Cellular biology of epileptogenesis. Lancet Neurology 2, 33–42.

Bazil, C.W., 2002. New antiepileptic drugs. The Neurologist 8, 71–81.

Bleakman, D., Gates, M.R., Ogden, A.M., Mackowiak, M., 2002. Kainate receptor agonists, antagonists and allosteric modulators. Current Pharmaceutical Design 8, 873–885.

Boulter, J., Hollmann, M., O'Shea-Greenfield, A., Hartley, M., Deneris, E., Maron, C., Heinemann, S., 1990. Molecular cloning and functional expression of glutamate receptor subunit genes. Science 249, 1033–1037.

Chittajallu, R., Braithwaite, S.P., Clarke, V.R., Henley, J.M., 1999. Kainate receptors: subunits, synaptic localization and function. Trends in Pharmacological Sciences 20, 26–35.

Chong, M.S., Libretto, S.E., 2003. The rationale and use of topiramate for treating neuropathic pain. Clinical Journal of Pain 19, 59–68.

Clarke, V.R., Ballyk, B.A., Hoo, K.H., Mandelzys, A., Pellizzari, A., Bath, C.P., Thomas, J., Sharpe, E.F., Davies, C.H., Ornstein, P.L., Schoepp, D.D., Kamboj, R.K., Collingridge, G.L., Lodge, D., Bleakman, D., 1997. A hippocampal GluR5 kainate receptor regulating inhibitory synaptic transmission. Nature 389, 599–603.

Cui, C., Mayer, M.L., 1999. Heteromeric kainate receptors formed by the coassembly of GluR5, GluR6 and GluR7. Journal of Neuroscience 19, 8281–8291.

Deckers, C.L., Knoester, P.D., de Haan, G.J., Keyser, A., Renier, W.O., Hekster, Y.A., 2003. Selection criteria for the clinical use of the newer antiepileptic drugs. CNS Drugs 17, 405–421.

Dodgson, S.J., Shank, R.P., Maryanoff, B.E., 2000. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. Epilepsia 41 (Suppl. 1), S35–S39.

EdmondsJr., ., H.L., Jiang, Y.D., Zhang, P.Y., Shank, R., 2001. Topiramate as a neuroprotectant in a rat model of global ischemia-induced neurodegeneration. Life Sciences 69, 2265–2277.

Ernst, C.L., Goldberg, J.F., 2003. Antidepressant properties of anticonvulsant drugs for bipolar disorder. Journal of Clinical Psychopharmacology 23, 182–192.

Fletcher, E.J., Lodge, D., 1996. New developments in the molecular pharmacology of α-amino-3-hydroxyisoxazole propionate and kainate receptors. Pharmacology & Therapeutics 70, 65–89.

Gale, K., 1988. Progression and generalization of seizure discharge: anatomical and neurochemical substrates. Epilepsia 29 (Suppl. 2), S15–S34.

Ghetti, A., Plata-Salaman, C.R., Shank, R.P., Heinemann, S., 2001. Effects of topiramate on kainate receptors. Society for Neuroscience Abstracts 27, Program No. 871.1.

Gibbs, III, ., J.W., Sombati, S., DeLorenzo, R.J., Coulter, D.A., 2000. Cellular actions of topiramate: blockade of kainate-evoked inward currents in cultured hippocampal neurons. Epilepsia 41 (Suppl. 1), S10–S16.

Gryder, D.S., Rogawski, M.A., 2003. Selective antagonism of GluR5 kainate receptor-mediated synaptic currents by topiramate in rat basolateral amygdala neurons. Journal of Neuroscience 23, 7069–7074.

Johnson, B.A., Ait-Daoud, N., Bowden, C.L., DiClemente, C.C., Roache, J.D., Lawson, K., Javors, M.A., Ma, J.Z., 2003. Oral topiramate for treatment of alcohol dependence: a randomised controlled trial. Lancet 361, 1677–1685.

Lauridsen, J., Honoré, T., Krogsgaard-Larsen, P., 1985. Ibotenic acid analogues. Synthesis, molecular flexibility, and in vitro activity of agonists and antagonists at central glutamic acid receptors. Journal of Medicinal Chemistry 28, 668–672.

Mulle, C., Sailer, A., Perez-Otano, I., Dickinson-Anson, H., Castillo, P.E., Bureau, I., Maron, C., Gage, F.H., Mann, J.R., Bettler, B., Heinemann, S.F., 1998. Altered synaptic physiology and reduced susceptibility to kainate-induced seizures in GluR6-deficient mice. Nature 392, 601–605.

Rogawski, M.A., 2002. Principles of antiepileptic drug action. In: Levy, R.H., Mattson, R.H., Meldrum, B.S., Perucca, E. (Eds.), Antiepileptic Drugs. fifth ed.. Lippincott Williams & Wilkins, Philadelphia, pp. 3–22.

Rogawski, M.A., Donevan, S.D., 1999. AMPA receptors in epilepsy and as targets for antiepileptic drugs. Advances in Neurology 79, 947–963.

Rogawski, M.A., Gryder, D., Castaneda, D., Yonekawa, W., Banks, M.K., Li, H., 2003. GluR5 kainate receptors, seizures, and the amygdala. Annals of the New York Academy of Sciences 985, 150–162.

Shank, R.P., Gardocki, J.F., Vaught, J.L., Davis, C.B., Schupsky, J.J., Raffa, R.B., Dodgson, S.J., Nortey, S.O., Maryanoff, B.E., 1994. Topiramate: preclinical evaluation of structurally novel anticonvulsant. Epilepsia 35, 450–460.

Shank, R.P., Gardocki, J.F., Streeter, A.J., Maryanoff, B.E., 2000. An overview of the preclinical aspects of topiramate: pharmacology, pharmacokinetics, and mechanism of action. Epilepsia 41 (Suppl. 1), S3–S9.

Singh, L., Oles, R.J., Vass, C.A., Woodruff, G.N., 1991. A slow intravenous infusion of *N*-methyl-DL-aspartate as a seizure model in the mouse. Journal of Neuroscience Methods 37, 227–232.

Skradski, S., White, H.S., 2000. Topiramate blocks kainate-evoked cobalt influx into cultured neurons. Epilepsia 41 (Suppl. 1), S45–S47.

Smith, L., Price-Jones, M., Hughes, K., Egebjerg, J., Poulsen, F., Wiberg, F.C., Shank, R.P., 2000. Effects of topiramate on kainate- and domoate-activated [^{14}C]guanidinium ion flux through GluR6 channels in transfected BHK cells using Cytostar-T scintillating microplates. Epilepsia 41 (Suppl. 1), S48–S51.

Smith-Swintosky, V.L., Zhao, B., Shank, R.P., Plata-Salaman, C.R., 2001. Topiramate promotes neurite outgrowth and recovery of function after nerve injury. NeuroReport 12, 1031–1034.

Smolders, I., Bortolotto, Z.A., Clarke, V.R., Warre, R., Khan, G.M., O'Neill, M.J., Ornstein, P.L., Bleakman, D., Ogden, A., Weiss, B., Stables, J.P., Ho, K.H., Ebinger, G., Collingridge, G.L., Lodge, D., Michotte, Y., 2002. Antagonists of GLU_{K5}-containing kainate receptors prevent pilocarpine-induced limbic seizures. Nature Neuroscience 5, 796–804.

Sommer, B., Burnashev, N., Verdoorn, T.A., Keinänen, K., Sakmann, B., Seeburg, P.H., 1992. A glutamate receptor channel with high affinity for domoate and kainate. EMBO Journal 11, 1651–1656.

Stein, E., Cox, J.A., Seeburg, P.H., Verdoorn, T.A., 1992. Complex pharmacological properties of recombinant α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptor subtypes. Molecular Pharmacology 42, 864–871.

Stensbøl, T.B., Borre, L., Johansen, T.N., Egebjerg, J., Madsen, U., Ebert, B., Krogsgaard-Larsen, P., 1999. Resolution, absolute stereochemistry and molecular pharmacology of the enantiomers of ATPA. European Journal of Pharmacology 380, 153–162.

Steppuhn, K.G., Turski, L., 1993. Modulation of the seizure threshold for excitatory amino acids in mice by antiepileptic drugs and chemoconvulsants. Journal of Pharmacology and Experimental Therapeutics 265, 1063–1070.

Swinyard, E., Woodhead, J., White, H., Franklin, M., 1989. General principles: experimental selection, quantification, and evaluation of anticonvulsants. In: Levy, R., Mattson, R., Meldrum, B., Penry, J., Dreifuss, F. (Eds.), Antiepileptic Drugs. Raven Press, New York, pp. 85–102.

Taverna, S., Sancini, G., Mantegazza, M., Franceschetti, S., Avanzini, G., 1999. Inhibition of transient and persistent Na^+ current fractions by the new anticonvulsant topiramate. Journal of Pharmacology and Experimental Therapeutics 288, 960–968.

Von Seggern, R.L., Mannix, L.K., Adelman, J.U., 2002. Efficacy of topiramate in migraine prophylaxis: a retrospective chart analysis. Headache 42, 804–809.

White, H.S., Brown, S.D., Woodhead, J.H., Skeen, G.A., Wolf, H.H., 1997. Topiramate enhances GABA-mediated chloride flux and GABA-evoked chloride currents in murine brain neurons and increases seizure threshold. Epilepsy Research 28, 167–179.

White, H.S., Brown, S.D., Woodhead, J.H., Skeen, G.A., Wolf, H.H., 2000. Topiramate modulates GABA-evoked currents in murine cortical neurons by a nonbenzodiazepine mechanism. Epilepsia 41 (Suppl. 1), S17–S20.

Yamashita, H., Ohno, K., Amada, Y., Hattori, H., Ozawa-Funatsu, Y., Toya, T., Inami, H., Shishikura, J.I., Sakamoto, S., Okada, M., Yamaguchi, T., 2004. Effects of 2-[*N*-(4-chlorophenyl)-*N*-methylamino]-4*H*-pyrido[3.2-*e*]-1,3-thiazin-4-one (YM928), an orally active α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist, in models of generalized epileptic seizure in mice and rats. Journal of Pharmacology and Experimental Therapeutics 308, 127–133.

Zhang, X., Velumian, A.A., Jones, O.T., Carlen, P.L., 2000. Modulation of high-voltage-activated calcium channels in dentate granule cells by topiramate. Epilepsia 41 (Suppl. 1), S52–S60.

Zona, C., Ciotti, M.T., Avoli, M., 1997. Topiramate attenuates voltage-gated sodium currents in rat cerebellar granule cells. Neuroscience Letters 231, 123–126.